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THE COMBINED USE OF ANTI-INFECTIVES AND ANTICOAGULANTS IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS*†**

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THE subject of subacute bacterial endocarditis requires few introductory remarks before an audience of The New York Academy of Medicine. Since 1906 and culminating with the publication of his monograph[1] in 1941, Emanuel Libman has described the clinical syndrome in all of its ramifications and clearly delineated the difficulties imposed upon the therapeutic attack; he established the fact that the disease, with few exceptions, was of streptococcal origin; he demonstrated, as far back as 1910, that it was possible to obtain positive blood cultures in 73 of his first 75 cases; he astutely assumed that the portal of infection was "about the teeth or their roots, the tonsils and accessory sinuses or other parts of the upper respiratory tract;" he stressed the importance of the previously existing valvular defect, whether acquired or congenital, as a predisposing factor in the production of the disease; he described fully the usual and the bizarre pathological changes asso-

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ciated with the disease; he emphasized, throughout his clinical thesis, the pathognomonic features particularly referable to the eruptive phenomena, changes in skin color, the frequent embolic complications and the wide range of forms in which the disease might masquerade.

Early in the course of his studies, Libman recognized that severer forms of the disease occasionally progressed to spontaneous recovery and estimated that this happy outcome was encountered in at most three to five per cent of the afflicted; he also recognized that there was a milder or bacteria-free stage of the disease in which the patient might not be seen until recovery had occurred. Emanuel Libman noted that an occasional recovery was reported using any one of a variety of chemotherapeutic or physiotherapeutic modalities. With his usual perspicacity, he cautioned that the lack of consistent effect from any one given remedial agent suggested that the isolated "cure" may have been more likely an instance of the spontaneous recovery that is occasionally noted in the severe forms or an example of the milder bacteria-free syndrome.

Emanuel Libman's monograph concludes with the statement of the status of therapy in 1941; in his own words, I quote, "at the present time, therapy in subacute bacterial endocarditis remains unsatisfactory. . . . A chemotherapeutic agent more effective on the streptococcus viridans than any at present available is needed and may be found; . . . The future looks more promising than ever before."

It is my purpose this evening to add a chapter to Libman's monograph; we shall present data which indicate that combined therapy using an anti-infective agent and an anticoagulant produced what appears to be clinical cure in approximately 75 per cent of a consecutive series of 54 unselected patients.

Laboratory Data

The basis of the present clinical investigation is dependent upon experimental thrombotic bacterial endocarditis as it was produced in the rabbit in collaboration with my colleagues Rosenblatt and Lederer.[2] This work indicated that fibrin and blood elements served as an impenetrable barrier to effective chemotherapeusis; the offending organisms, lying deep in the vegetation, were well protected from circulating anti-infective agents. To accomplish disappearance of vegetations, the combined use of a suitable chemotherapeutic agent and an anticoagulant

was required. Heparin was successfully employed, in these experimental animals, to arrest the deposition of blood platelets and fibrin which served as a protective nidus and as a stimulus for bacterial growth; relatively fresh, artificially induced thrombi in the animal could be dissipated following the use of the anticoagulants. In corroboration of the experimental investigations, were observations obtained from human post-mortem material which indicated that heparin has a possible erosive effect on endocardial vegetations.[3]

Evolution of the Clinical Studies

The attempt to translate experimental investigation into terms of clinical therapeusis was at first disappointingly unsuccessful. The intravenous administration of heparin was fraught with danger and the expense was prohibitive in many instances. Whether given by continuous venoclysis or fractional intravenous injection, heparin therapy was cumbersome, accompanied by severe reactions and associated with treatment deaths in altogether too many instances to justify its continuance.[4] To overcome these shortcomings, a special method[5] was devised for the subcutaneous deposition of the drug, through adoption of the Pitkin menstruum, composed of gelatine, dextrose, glacial acetic acid and water in definite proportions, which was developed to regulate the rate of release of water-soluble drugs injected intramuscularly or subcutaneously. By this technique, a slower and more equable absorption of heparin was accomplished.

When this portion of the clinical technique had been solved, a combined attack was inaugurated using the sulfonamides in association with the heparin. A group of seventeen patients with subacute bacterial endocarditis was treated but there was no more than two apparently authentic "cures"—insufficient to justify the conclusion that a specific therapeutic result had been obtained beyond what might be noted with the occasional spontaneous cure or the development of Libman's bacteria-free state. Nevertheless, the two successful issues were sufficient to justify a continued project, more particularly since one of the necropsied cases showed an apparent diminution in the size of vegetations which were smaller and more discontinuous than might have been anticipated.

With the introduction of penicillin therapy, we were sufficiently fortunate to obtain supplies through the courtesy of Mr. John L. Smith

TABLE I

USE OF HEPARIN IN PENICILLIN ASSAYS

Experiment #1 (1-4-44)

	ml. Penicillin Solution		*mg. Heparin*	*mg. Heparin-O.U. ratio in 10 ml.*	*Series-Dilution Test Results*
A.	9	+	0.5 in 1 ml. H_2O	0.5 mg./1,120 O.U.	124 O.U./ml.
B.	9	+	1.0 " " " "	1.0 " " "	145 " "
C.	9	+	5.0 " " " "	5.0 " " "	145 " "
D.	9	+	10.0 " " " "	10.0 " " "	124 " "
Control	9	+	1.0 ml. H_2O		126 O.U./ml.

Experiment #2 (1-8-44)

	ml. Penicillin Solution		*mg. Heparin*	*mg. Heparin-O.U. ratio in 6 ml.*	*Series-Dilution Test Results*
A.	5	+	0.5 in 1 ml. H_2O	0.5 mg./640 O.U.	128 O.U./ml.
B.	5	+	1.0 " " " "	1.0 " " "	128 " "
C.	5	+	5.0 " " " "	5.0 " " "	135 " "
D.	5	+	10.0 " " " "	10.0 " " "	128 " "
Control	5	+	1.0 ml. H_2O		128 O.U./ml.

of the Charles Pfizer Company and later, also, through the coöperation of the Committee on Penicillin Therapy of the National Research Council under the aegis of Dr. Chester S. Keefer. The technique was modified by the replacement of sulfonamide with penicillin; continuation of subcutaneous depositions of heparin was made possible by the coöperation of Ralph D. Shaner and Leo Pirk of Roche-Organon, Inc., which company gratuitously furnished all heparin preparations.

As a preliminary to the inauguration of penicillin-heparin therapy, experiments were devised to determine the effects of heparin on solutions of penicillin. The data (Table I) indicated clearly that the anticoagulant had no measurable effect on the anti-infective potentialities of the penicillin; indeed, there was some suggestion of possible synergism or potentiation.

DOSAGE SCHEDULE

The administration of heparin and the determination of optimum

TABLE II

TREATMENT STATISTICS—SUMMARY

Dosage		
Penicillin sodium salt (Oxford units)		
	Range	
	Low	*High*
Daily dosage	40,000 to	1,000,000
Total dosage	867,000 to	48,930,000
Heparin sodium salt (milligrams)		
Total dosage	400 to	11,500

COURSES OF PENICILLIN—HEPARIN THERAPY

Number of courses required in each case of the successfully treated group.

No. of courses	*No. of Patients*
1	27
2	8
3	4
4	1
Total	40

dosage are easily gauged by the tilt-tube Lee White modification of Howell's method[6] for determining blood coagulation time. A reading of 30 to 60 minutes is regarded as satisfactory evidence of an effectual anticoagulant level. Coagulation times above one hour are wasteful of the drug and may indeed be hazardous, particularly if the clotting time is prolonged to two or more hours. Effectually to heparinize the blood, necessitates subcutaneous deposits of 300 mg. every second or third day or approximately 200 mg. daily of the aqueous commercial product when incorporated in the venoclysis. Hyper-reactors require lesser amounts of heparin and hypo-reactors need additional dosage.

The estimation of penicillin dosage presents greater difficulty and requires the coöperation of the laboratory. Probatory sensitivity tests must be done on the offending organism. In general, the causative agents are inhibited within the dilutions of 0.007 to .5 Oxford units of penicillin per cc. of test broth. Under these circumstances, the daily

dosage of penicillin (Table II) varies from 40,000 to 1,000,000 Oxford units; total individual unitage may range between the low of 867,000 and a high of 48,930,000 Oxford units. It may be observed parenthetically, as a tribute to the nontoxicity of the presently available preparations of penicillin, that the latter amount could be introduced without significant toxicologic phenomena.

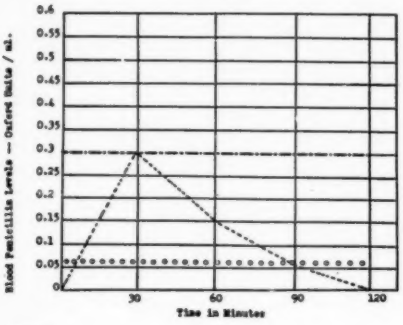
At the outset, through limitations in the supply of penicillin, an effort was made to reduce the span of treatment to an absolute minimum so that material might be available for as many patients as possible. Originally, a two week course of treatment was projected and was actually found adequate for the accomplishment of the disappearance of early endocardial lesions. Unfortunately, this two week course alone was insufficient for patients who had been ill for longer periods of time and a three week course was regarded as essential for those who had been ill for two to four months; a four week course was believed necessary for those who had had the disease for more than four months. It is our present opinion that our current practice of a five week course must be made the standard minimum when the supplies of penicillin justify treating the individual patient in optimum fashion. Additional courses are given whenever necessary and are well tolerated. Multiple courses are not uncommon in the advanced cases.

Based on penicillin-sensitivity tests, it appears that an average daily dose of at least 200,000 Oxford units is required. Increased dosage or a more prolonged span of treatment is necessary for patients who are deteriorated, or who show severe clinical manifestations of bacterial activity such as embolization, marked splenomegaly and violent temperature reactions. Additional factors that enter into the determination of the dosage level are the sensitivity of the offending organism to penicillin and the capacity of the patient to develop and maintain an adequate level of the anti-infective agent in the blood.[7] To be therapeutically effective, penicillin blood levels must be far in excess of the in vitro bactericidal requirements; the best clinical results are achieved when the average unitage of penicillin is sufficient to develop and maintain a blood serum level of five to ten times the sensitivity figure. Inadequate dosage invites treatment failure and the organisms may acquire resistance that is so high as to render future therapeutic levels virtually unattainable. In at least one instance, we observed a forty-fold increase in the resistance of the organism to penicillin.

COMPARATIVE EFFECTIVENESS OF FRACTIONAL INTRAMUSCULAR PENICILLIN THERAPY VERSUS CONTINUOUS VENOCLYSIS.

Total Daily Dosage = 240,000 Oxford Units.

GRAPH I

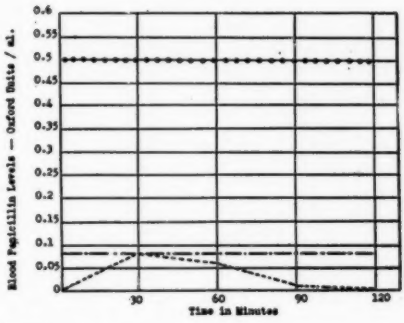


KEY:

Patient A. C. #39, Successfully treated.

000000 — Sensitivity of Organism
—.—. — Intravenous Penicillin Level
----- — Intramuscular Penicillin Level

GRAPH II



KEY:

Patient S. G. #59, Refractory case.

000000 — Sensitivity of Organism
—.—. — Intravenous Penicillin Level
----- — Intramuscular Penicillin Level

GRAPH I—*Patient A. C.*—Streptococcus viridans inhibited by 0.06 O.U. per cc. test broth. Daily continuous intravenous of 240,000 O.U. of penicillin achieved blood level of 0.3 per cc. of serum. 20,000 O.U. given intramuscularly every two hours (totalling 240,000 O.U. per day) attained the intravenous blood level for only a small fraction of the treatment period. During the latter part of the two hour period there was no detectable amount of penicillin in the blood serum. This patient responded satisfactorily to one three week course of penicillin, 240,000 O.U. daily by continuous venoclysis with heparin in sufficient amounts to maintain coagulation time between 30 and 60 minutes.

GRAPH II—*Patient S. G.*—Streptococcus viridans inhibited by 0.5 O.U. per cc. test broth (very resistant type). Neither continuous intravenous nor fractional intramuscular administration of penicillin in daily dosages of 240,000 O.U. achieved therapeutic levels. It was impossible to attain satisfactory levels even when the penicillin was stepped up to 1,000,000 O.U. per day. This case was extremely refractory to treatment.

THE TECHNIQUE OF TREATMENT

It is our custom to devote the first few days of therapy to the determination of penicillin levels following intramuscular and intravenous administration of the drug. During this probatory period, heparin is withheld primarily to obviate any dislodgement of loosely attached vegetations.

Our experiences indicate that intravenous injection of penicillin is decidedly the method of choice; intramuscular injections result in the attainment of a higher peak which cannot be maintained and which is

TABLE III

REACTIONS OCCURRING DURING THERAPY—SUMMARY

	Chills and Fever	*Fever*	*Local Pain*	*Regional Angiitis*	*Regional Adenopathy*	*Urticaria*	*Vesicular Eruptions*
Penicillin Intravenous	Rare	Rare	0	Frequent	0	Occasional	Occasional
Penicillin Intramuscular	0	0	Common, degree Variable	0	Occasional	0	0
Heparin Subcutaneous	0	Common	Common, degree Variable	0	Occasional	0	0
Heparin Intravenous	0	Common	0	0	0	0	0
Penicillin and Heparin Combined	Not Uncommon*	Common	Uncommon	Occasional	Uncommon	Occasional	Occasional

* Causative factor(s) not clear.

followed by a prompt and abrupt decline so that, for a sizable fraction of the treatment day, the blood is virtually free of detectable amounts of penicillin (Graph I, II). In contrast, the intravenous injection produces a constant and sustained level. Only rarely, when the patient is in congestive failure so that the additional intravenous administration of the bulk of fluid seems more than the circulation can maintain, do we resort to intramuscular introduction; at the earliest possible moment then, we revert to the continuous intravenous drip employing minimum amounts of diluent. In all instances, when available, Ringer's solution is employed as the vehicle; the patient is placed on a salt-poor intake and heparin is deposited subcutaneously as soon as the preliminary steps have been completed.

Accessory therapeutic measures include the use of high caloric, high vitamin diets, supplementary multivitamin preparations, the use of hematinics in liberal dosage where there is anemia and the resort to frequent transfusions when indicated. The latter require temporary

interruption of heparinization and hence are postponed, if possible, till the termination of treatment.

Toxicity

Reactions to treatment (Table III) occur frequently. Those of minor importance include chills, fever, local pain, regional angiitis, regional adenopathy, urticaria and vesicular eruptions.

Febrile reactions are rather common and may be ascribed to a variety of factors. There are the obvious pyrogenic factors such as airborne contaminants. This is controlled by using sterisol bottles and periodic refrigeration. The substitution of viscose instead of rubber tubing eliminates a small fraction of reactions but does not justify its universal use. The incidence of troublesome regional angiitis with its attendant rigors and sharp rises in temperature can be reduced by changing veins and apparatus every 3-4 days. Wherever possible a vein about the wrist or forearm is used to allow freedom of movement.

Thrombophlebitis seldom occurred in our heparinized patients even when this was a troublesome complication of the early penicillin era. Elaborate immunologic tests done with early crude and progressively purer products of penicillin have failed to elicit any instance of allergy in any of our patients despite multiple courses of intensive and extensive therapy.

Febrile reactions due to heparin are frequent, for the most part due to excessive anticoagulant activity. These are overcome readily by the mere withdrawal of the drug. One patient under combined penicillin-heparin therapy developed clinical manifestations of sensitivity to heparin. Attempts to resume the conjoint therapy were followed by episodes of chills and fever, the last one being associated with generalized urticaria. Intracutaneous tests were negative to penicillin but gave a moderate reaction to heparin. He has since received as much as 1,000,000 Oxford units of penicillin daily intravenously for some weeks without untoward reactions.

Urticaria has, at times, been troublesome, mostly post-therapy, and is almost invariably attributable to penicillin.

Results of Therapy

The results of therapy (Table IV) of subacute bacterial endocarditis, using the combination of the intravenous introduction of the

TABLE IV

RESULTS WITH PENICILLIN-HEPARIN IN SUBACUTE BACTERIAL ENDOCARDITIS

Total No. of Cases (Consecutive and Unselected)		54	100%
Duration of illness prior to Penicillin-Heparin Therapy (Weeks)	1 to 78		
Penicillin sensitivity of causative organisms (Oxford Units)	0.007 to 0.5		
No. of cases in which therapy was successful		40	74%
Patients Living	37		
Patients Deceased—Other Causes	3		
Post-Therapy Period of Observation (months)	2 to 15		
No. of cases in which therapy failed		14	26%

TABLE V

ANALYSIS OF FACTORS IN FAILURES OF PENICILLIN-HEPARIN THERAPY—SUMMARY

	No. of Cases	*Percentage*
1. Patient Factors		
a. Cardiac failure	4	28.5
b. Cerebral embolism	3	21.4
c. Inanition	1	7.2
d. Intercurrent infection	2	14.3
2. Organism-Resistant	3	21.4
3. Reinfection	1	7.2
Total	14	100.0

anti-infective agent and mostly subcutaneous implants of the anticoagulant, have been tabulated according to the records of 54 consecutive and unselected patients. Many of our patients were in pitiful condition when therapy was inaugurated. In certain instances, congestive failure had reduced them to the point where any form of therapy was associated with considerable hazard. Other patients were in the ulcerative phase of the endocardial disease and were throwing off emboli from

friable and necrotic vegetations. Despite the precarious manifestations of many of the afflicted, we had no choice other than to inaugurate therapy, since refusal was tantamount to the imposition of a death sentence. Had we chosen to treat only those patients in the earlier stages of the disease and to eliminate those with manifestations of circulatory failure, ulcerative lesions, and embolic complications, a considerably higher incidence of favorable accomplishment might have been recorded.

As the records now stand, 54 patients were treated by combination of anti-infective, anticoagulant therapy. The duration of illness prior to treatment varied from one to seventy-eight weeks; the penicillin sensitivity of the etiological organism varied from 0.007 to 0.5 Oxford units, sensitive to resistant. Fourteen, or 26 per cent of the group are recorded as failures; 40, or 74 per cent may be regarded as satisfactory results. In the latter group, 37 of the 40 are alive and many have resumed useful occupations; 3 have died of other causes. In the group of treatment failures, there have been 13 deaths from progressive circulatory failure, coronary occlusion, embolization and lobar pneumonia, or a total of 16 fatalities in the original roster of 54 cases.

Treatment Failure

Treatment failure may be attributed to patient factors, refractoriness of the organism or reinfection with the same or another strain of streptococcus.

Of the 14 treatment failures (Table V), it is our opinion that 10 might be attributed to inability of the patient to withstand the ravages of the infection and to utilize the full benefits of combined anti-infective, anticoagulant therapy. At least 4 of the patients suffered from circulatory failure, 3 encountered cerebral embolizations, 1 had profound inanition and 2 had intercurrent infections, notably, lobar pneumonia.

A second cause for treatment failure in 3 patients was the refractoriness of the organism. In unreported studies (Table VI) made by J. M. Sherman of Cornell University, an attempt was made to establish a correlation between streptococcus typing, penicillin sensitivity and the clinical response. In our series of 54 patients, Sherman worked with 13 different organisms and established the presence of three different species. Three patients, infected with a previously unidentified streptococcus, were resistant to therapy and all three succumbed. The

TABLE VI

VARIETY OF STREPTOCOCCUS AS A POSSIBLE INFLUENCE ON PROGNOSIS

Preliminary Report on Work in Progress
(Kindness of Prof. J. M. Sherman, Cornell University)

Causative Organism	*No. of Cases*	*Treatment Successful*	*Reinfection*	*Fatal Outcome*
Streptococcus sp.	4	0	1	3
Streptococcus mitis	7	6	0	1
Streptococcus bovis	2	2*	0	0
Total	13	8	1	4

Streptococcus sp.: Apparently a new and distinct variety of streptococcus. Strains belonging to this variety show rather homogenous cultural and biochemical reactions.

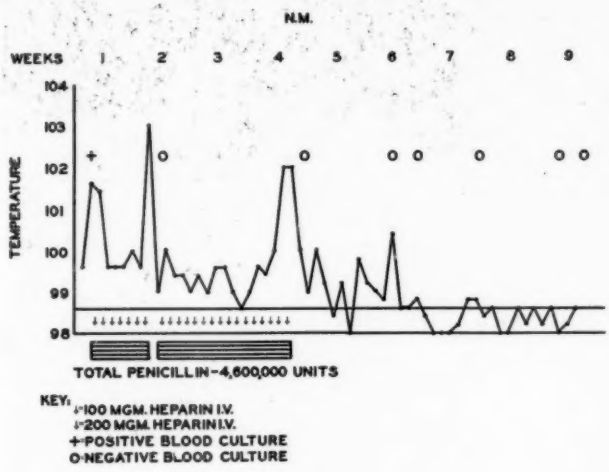
Streptococcus mitis: The common throat viridans streptococcus.

Streptococcus bovis: Similar to so-called "Bargen streptococcus."

* One of these patients, N.M.—Case 32, subsequently died of heart failure. No evidence of bacterial activity at autopsy.

blood of 7 patients disclosed a Streptococcus mitis, apparently more sensitive to penicillin since 6 of the 7 recovered and there was but one fatality; the remaining two victims were infected by Streptococcus bovis and one of these recovered while the other died. Significantly, the autopsy on the fatal Streptococcus bovis infection revealed evidences of a healed endocarditis.

The last treatment failure in a surviving patient is an instance of reinfection with another strain of streptococcus. Studies by J. M. Sherman indicate that the organisms recovered from the blood stream during the initial and subsequent attack are different. This suggests that the patient was cured of his disease, but not necessarily immunized to subsequent bacterial invasion. The original strain is Streptococcus salivarius, whereas the more recent strain is significantly the unidentified streptococcus found, as previously mentioned, only in patients who were resistant to therapy. It will be especially interesting to observe the response to the current course of treatment.



GRAPH III

DEATHS

In the series of the 54 original patients, there were 16 deaths. Thirteen of the deaths occurred in the group of treatment failures as previously indicated, three of the fatal issues occurred in those who had been satisfactorily treated. The autopsies of two of the satisfactorily treated patients have afforded an interesting insight into the disputed problem of a temporary sterilization of the blood versus actual cure. Evidence in favor of actual cure is afforded by the descriptions of the heart valve as recorded in one instance by E. S. Maxwell of the Good Samaritan Hospital in Sterling, Kentucky, and in the other by J. W. Denton and A. F. Heyl of the New Rochelle Hospital.

Case–N.M. (Graph III), age 29, female: Subacute bacterial endocarditis, 12 weeks; Streptococcus viridans (penicillin sensitivity 0.031 O.U.): chronic rheumatic cardiovalvular disease, aortic; aphasic on admission due to cerebral embolus; responded well to one 23 day course of penicillin-heparin therapy; developed intractable congestive heart failure which resisted all therapy; blood stream sterile for more than six months until death. Maxwell reports, in this case, that the right aortic cusp was almost completely destroyed and replaced by short fibrotic stubs. A congenital aneurysm was present near the origin of the aorta. It was Maxwell's opinion that death was due to cardiac failure

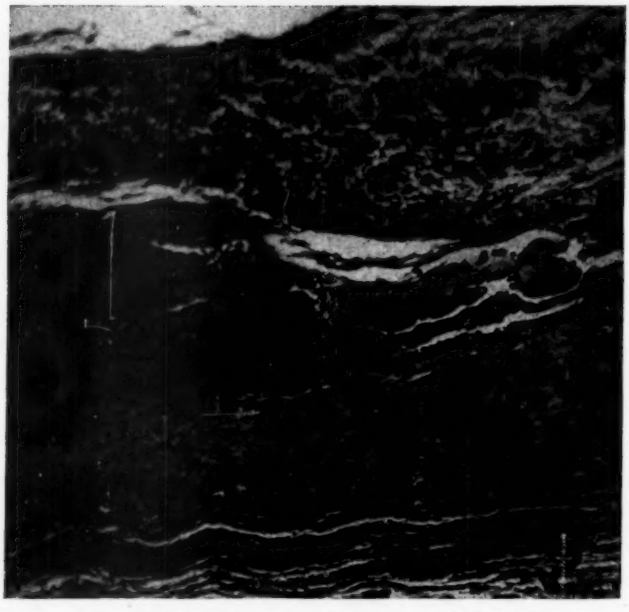
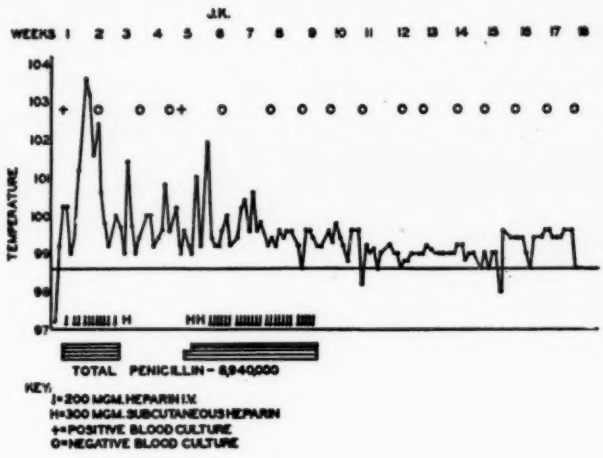


Fig. 1—*Aortic Valve*—Note stump-shaped cusp which is fibrotic and completely endothelialized.

Fig. 2—*Stump of Aortic Cusp*—(Higher magnification) note that there is no evidence of active inflammation or any indication of bacterial activity.

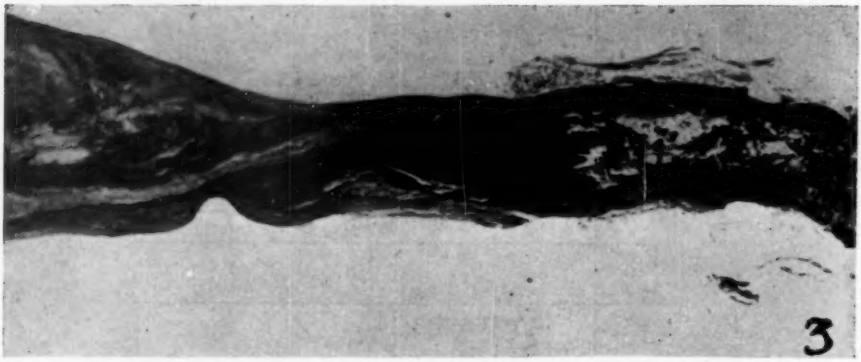


GRAPH IV

with marked visceral passive congestion. Histologic study showed fibrosis and hyalinization of the aortic stubs with no evidence of bacterial inflammation (Fig. 1, 2).

Case–J.K. (Graph IV), age 33, female: Subacute bacterial endocarditis, 28 weeks; Streptococcus viridans; chronic rheumatic cardiovalvular disease, aortic and mitral; two courses of penicillin-heparin therapy, 14 and 28 days respectively; discharged from hospital in mild congestive heart failure which progressed unfavorably, clinical behavior same as Case N.M.; blood stream sterile for more than three months until death. In this case autopsied by Denton and Heyl, they reported that there was a shredded, partially calcified anterior cusp of the aortic valve with marked insufficiency of the orifice. The heart was hypertrophied and dilated. There was severe chronic passive congestion of the viscera. It was the opinion of the pathologist that death was due to congestive heart failure and there were no histological evidences of active bacterial endocarditis (Fig. 3, 4).

Interpretation of autopsy findings and the evaluation of gross pathological phenomena invite a discussion also of the significance of embolization occurring during the course of treatment. It is a well-established fact that embolization is a common complication of subacute bacterial endocarditis, but embolization has also been attributed to heparinization, particularly in the presence of thrombotic vegetations



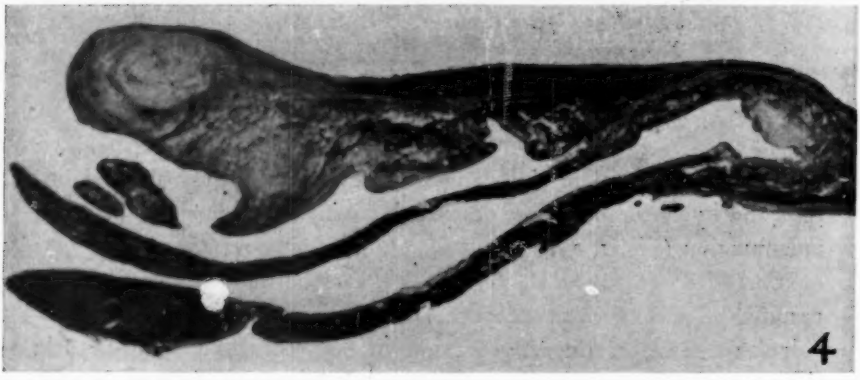


Fig. 3—*Aortic Valve*—Note the dense fibrotic character of the stroma and central fragmentation of the connective tissue. Note that the surfaces are completely endothelialized.

Fig. 4—*Mitral Valve Nodule*—Note composition of moderately cellular fibrous tissue. There is no evidence of active inflammatory change.

TABLE VII

GROSS EMBOLIC INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM

Time Of Occurrence With Respect to Penicillin-Heparin Therapy	*Number of Cases*	*Successfully Treated*	*Fatal Outcome*
Before treatment	4	4	
During treatment	3		3
After completion of treatment	1	1	
TOTAL	8	5	3

on the heart valves. To clarify this point, we have charted (Table VII) the relationship of embolization to therapy in eight of our patients. In four, embolic phenomena were present before the inauguration of treatment and four of these patients were successfully treated. Three patients in the first 30 of the series of 54 cases had embolization during treatment and succumbed. These are included among the treatment failures. It may be more than fortuitous that since introducing a probatory 3 day course of intramuscular penicillin treatment, there has been no intra-therapy cerebral embolization. In only one instance has there been a post-therapy embolization and that occurred in a patient who made a splendid recovery both from the infection and from the hemiplegia that resulted from the vascular occlusion. From these figures it would seem fair to conclude that pre-treatment embolization is not a contraindication to the inauguration of anticoagulant, anti-infective therapy and that embolization occurring during and following treatment is more likely a manifestation of the continued progress of the underlying disease than a result of the utilization of the anticoagulant.

Satisfactory Results

We have recorded 40 satisfactory results of whom 37 patients are still alive, many having resumed their normal activities. The most recent patient has been observed for only two months, but the oldest member of the group was discharged from the hospital fifteen months ago. In the favorable instance, the temperature falls to a normal level, the patient experiences a sense of well-being though, naturally, the mechanical deformities of the heart valves result in varying degrees of diminution in cardiac reserve. As in the instance of fatalities and treatment failures, the outcome of therapy is dependent upon patient and organism factors. Those patients who are seen soon after the onset of their bacteriemia, who have relatively small vegetations, who do not suffer from ulcerative endocarditis or circulatory failure have the optimum chance for cure, provided that their infection is by a penicillin-sensitive organism. The second variable, so clearly delineated by Sherman's studies (Table VI), deals with the variety of infecting organisms. Apparently, infection with Streptococcus mitis or bovis carries a considerably more favorable prognosis than an invasion caused by the special streptococcus which is presently being subjected to searching inquiry by Sherman. The accomplishment of a favorable outcome in approximately

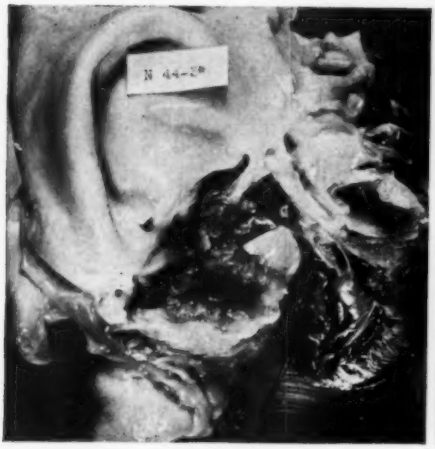
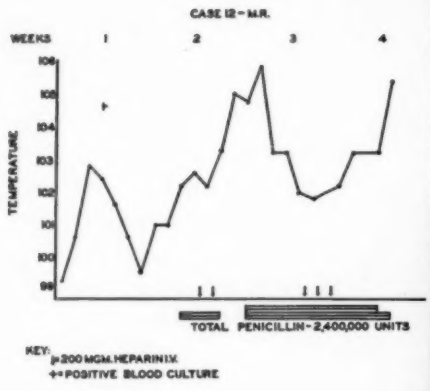


Figure 5

Figure 6



GRAPH V

Figure 7

Fig. 5—*Aneurysm of Sinus of Valsalva* viewed from above. Note severe ulcerative lesion.

Fig. 6—*Aortic and Mitral Thrombo-Ulcerative Endocarditis.* Note extensive myomalacia cordis, especially on cut surface.

Fig. 7—*Myomalacia Cordis*—Gross fragmentation of the myocardium.

3 out of every 4 patients leaves no doubt that the beneficial results observed in this unselected series cannot be attributed to spontaneous recovery. The severity of the manifestations of the disease in our group of patients precludes the possibility that we have been dealing with the bacteria-free stage of the subacute streptococcus endocarditis syndrome.

Prophylaxis

Consistent with Libman's observation concerning the possible portal of entry in the upper respiratory passages and the teeth, we have included in our treatment program the elimination of foci of infection before permitting the patient to leave the hospital. To prevent a recurrence of exacerbation of the bacteriemia, penicillin is administered parenterally and topically before and after the eradication of the focus.

It may be possible to illustrate the general principles which have been established through a concrete study of individual case records.

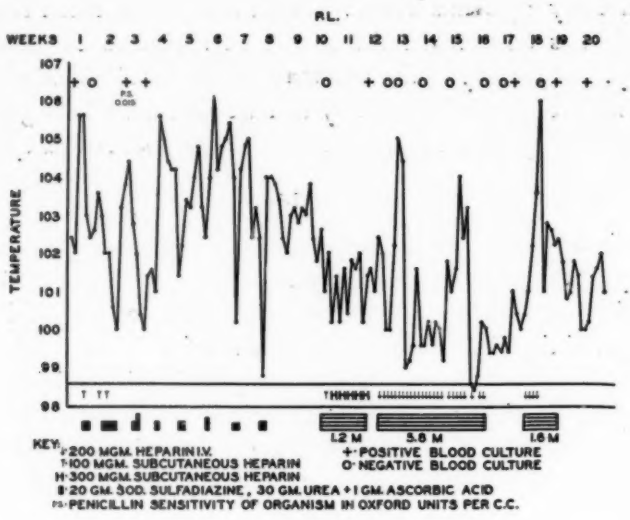
A. Analysis of Failure

1. *Example of Therapeutic Failure due to Patient Factors*

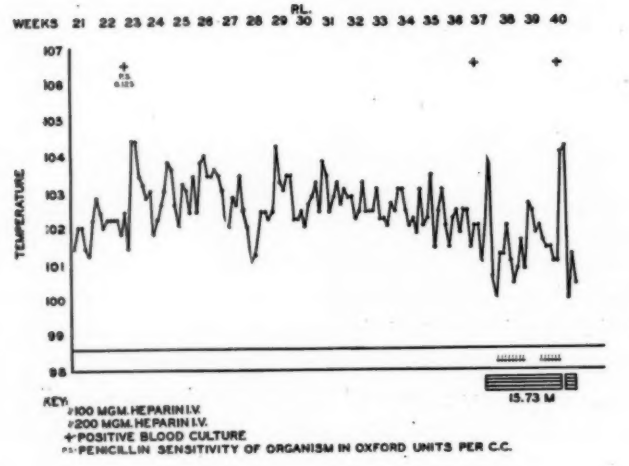
Case–M.R. (Graph V), age 47, male: Subacute bacterial endocarditis, 6 weeks; Streptococcus viridans; chronic rheumatic cardiovalvular disease, aortic and mitral; discontinuous therapy for 12 days, severe myocardial embarrassment, pulmonary and cerebral embolization; progressive downhill course, death from circulatory failure (Fig. 5, 6, 7).

2. *Example of Failure due to Organism Factor. Infection with Streptococcus sp. (Table VI).*

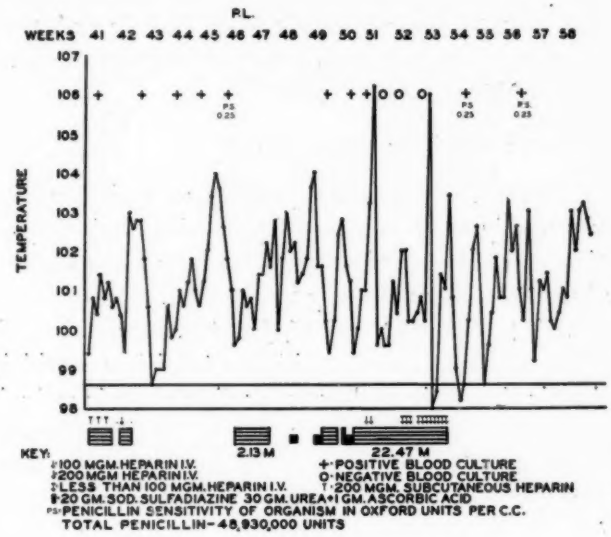
Case–P.L. (Graphs VI, VII, VIII), age 21, male: Subacute bacterial endocarditis; 56 weeks; Streptococcus viridans (penicillin sensitivity 0.015 to 0.25 O.U.): chronic rheumatic cardiovalvular disease, aortic and mitral; three courses of penicillin-heparin therapy with but temporary improvement; treatment suspended October 31, 1943 for lack of material; resumed four months later with intensive massive medication; therapy interrupted because of extra-cardiac complications which caused death despite total of 48,930,000 Oxford units given in six courses; organisms recovered after successive courses displayed increasing resistance to penicillin as shown in laboratory assays and reflected by the lack of clinical response; confirmatory autopsy findings were "thrombo-ulcerative mitral and aortic endocarditis, with lesions



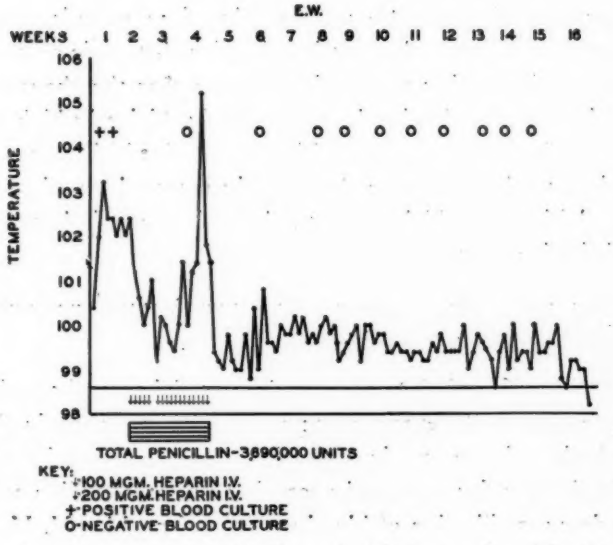
GRAPH VI



GRAPH VII



GRAPH VIII



GRAPH IX

predominantly aortic. Valve stenotic and insufficient. Chronic cardiac failure with accumulation of fluid in body cavities and passive congestion of viscera. Death due to ruptured esophageal varices. Long standing case with resistant organism."

B. CO-EXISTENT RHEUMATIC VIRUS ACTIVITY

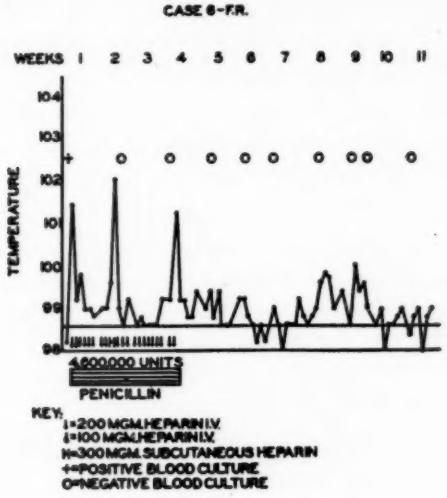
Penicillin treated patients are apparently susceptible to virus infections, due probably to disturbance of protective barriers by the drug. Reactivation of rheumatic virus in successfully treated patients with subacute bacterial endocarditis may be explained on the same basis.

Case–E.W. (Graph IX), age 16, female: Subacute bacterial endocarditis; 8 weeks; Streptococcus viridans (penicillin sensitivity 0.015 O.U.); chronic rheumatic cardiovalvular disease, aortic and mitral; one 17 day course of penicillin-heparin therapy sterilized blood stream; continued low grade temperature and elevated ESR, post-therapy, due to persistent rheumatic virus activity uncovered by successful therapy of S.B.E.; confirmatory electrocardiographic findings of protracted rheumatic virus activity; culmination in severe rheumatic pericarditis with effusion six months post-therapy; development of hydro-pneumopericardium and its subsequent disappearance portrayed radiographically; despite all this no recurrence of bacterial endocarditis; blood stream sterile for over nine months; weight gain of 14 pounds, hemoglobin 82 per cent, ESR 40 mm/hr; continued active rheumatic suspect.

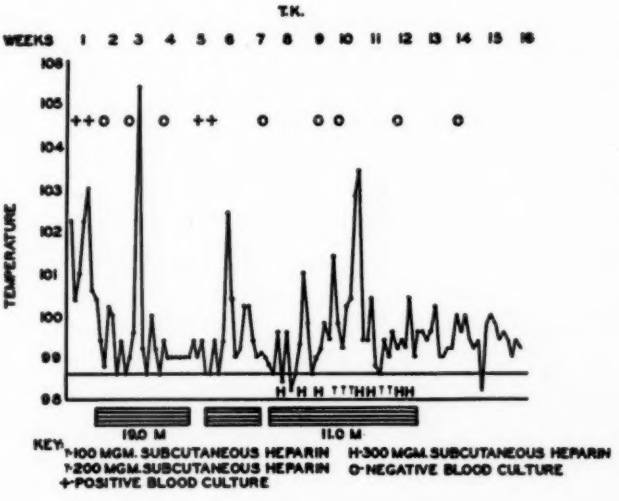
It was an interesting observation to note that the rheumatic virus continued to operate despite the presence of sufficiently high penicillin levels to eliminate streptococcal viridans bacteriemia. This and kindred observations tend to point up the recently reported experiences of the Army and Navy[8, 9] which attest to the resistance of rheumatic virus to anti-infective agents.

C. FAILURE WITH PENICILLIN ALONE–SUCCESS WITH COMBINED PENICILLIN-HEPARIN. Seven such instances to date.

Case–F.R. (Graph X), age 43, female: Subacute bacterial endocarditis, 12 months; Streptococcus non-hemolyticus; chronic rheumatic cardiovalvular disease, aortic and mitral; on fractional intramuscular penicillin therapy for 10 months totalling almost 9 million units with but transitory sterilization of blood stream; referred by M. H. Dawson and W. Goldring for penicillin-heparin therapy; one course interrupted



GRAPH X



GRAPH XI

after 3 weeks because of apparent penicillin-heparin sensitivity; striking progressive clinical improvement; no clinical or laboratory evidence of bacterial activity for over 10 months despite complicating upper respiratory infection; prophylactic oral surgery.

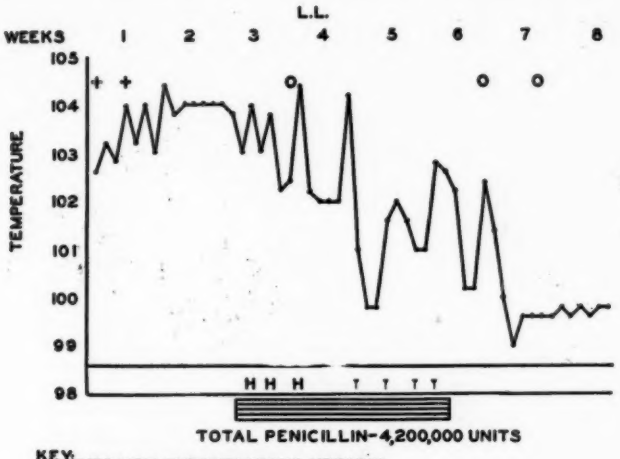
Case–T.K. (Graph XI), age 22, male: Subacute bacterial endocarditis, 3 weeks; Streptococcus viridans (penicillin sensitivity 0.03 O.U.); congenital cardiac lesion; recovery from subacute bacterial endocarditis 2 years ago following sulfonamide-fever therapy; two courses of penicillin per se, totalling 19 million Oxford units ineffective for present reinfection; one five week course of penicillin-heparin, with lower dosage of penicillin, successful; no clinical or laboratory evidence of bacterial activity for over 2 months.

D. COMPARATIVE RESPONSE OF PATIENTS TO THERAPY

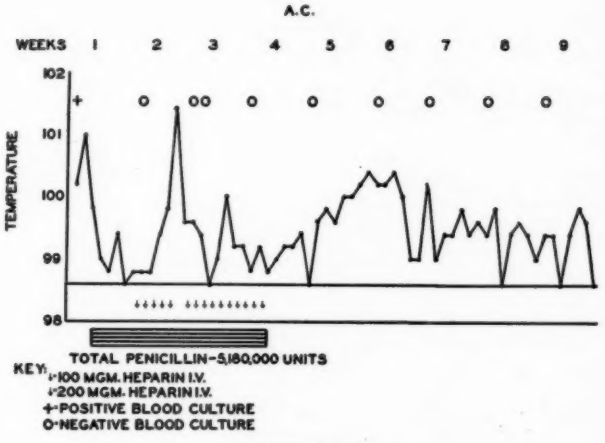
Case–L.L. (Graph XII), age 33, female: Mt. Sinai Hospital (courtesy of B. S. Oppenheimer): Subacute bacterial endocarditis, eight weeks; Streptococcus viridans (penicillin sensitivity 0.03 O.U.); chronic rheumatic cardiovalvular disease, mitral: stormy course characterized by rigors, spiking temperature; continuous intravenous medication impossible because of congestive heart failure necessitating dehydration measures; temperature immediately post-therapy ascribed to rheumatic virus activity, prompt response to salicylate therapy; infected dental foci removed; no clinical or laboratory evidence of bacterial activity for over 7 months; present weight 124 pounds, hemoglobin 80 per cent; ESR 7 mm/hr.

Case–A.C. (Graph XIII), age 59, male: Subacute bacterial endocarditis, 3 weeks; Streptococcus viridans (penicillin sensitivity 0.06 O.U.): chronic rheumatic cardiovalvular disease, mitral: therapy well tolerated; uneventful course apart from regional lymphangitis; no clinical or laboratory evidence of bacterial activity for over 5 months. Prophylactic oral surgery.

Case–H.T. (Graph XIV), age 27, male: Subacute bacterial endocarditis, 24 weeks, Streptococcus viridans (penicillin sensitivity 0.06 O.U.): chronic rheumatic cardiovalvular disease, aortic and mitral; intensive sulfonamide therapy ineffective, admitted for penicillin-heparin therapy; advanced case, deteriorated, glomerulonephritis, hemoglobin 45 per cent; marked febrile response after 14 days therapy; widespread simultaneous embolization to brain, lungs, spleen and kidneys due ap-

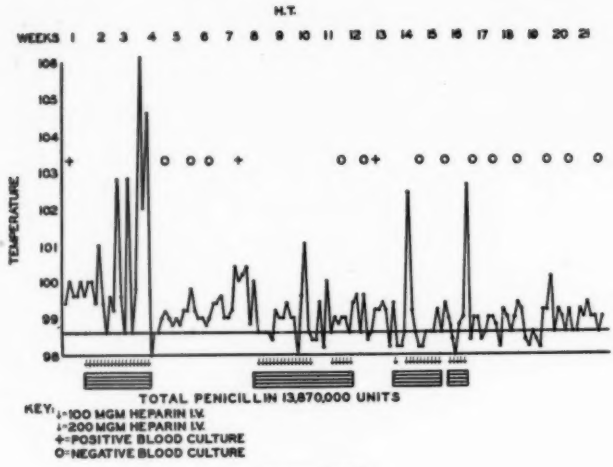


GRAPH XII

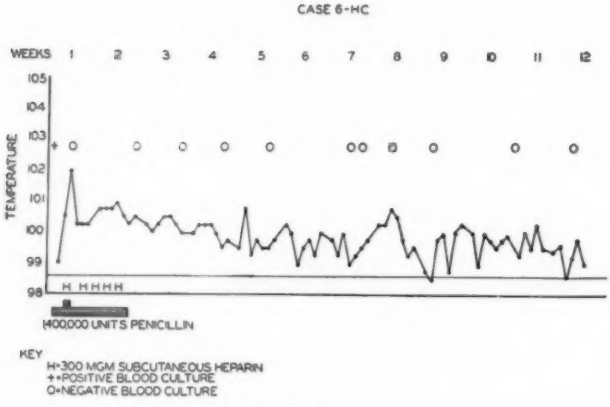


GRAPH XIII

parently to fragmentation of vegetations; prompt cessation of embolic phenomena and abrupt defervescence following suspension of therapy after 17 days; second and third courses of penicillin and heparin well tolerated; compare penicillin requirements with previous cases; progressive clinical improvement; no clinical or laboratory evidence of


H.T.
WEEKS 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
TEMPERATURE
TOTAL PENICILLIN 13,870,000 UNITS
KEY: ↓=100 MGM HEPARIN I.V.
↓=200 MGM HEPARIN I.V.
+=POSITIVE BLOOD CULTURE
O=NEGATIVE BLOOD CULTURE

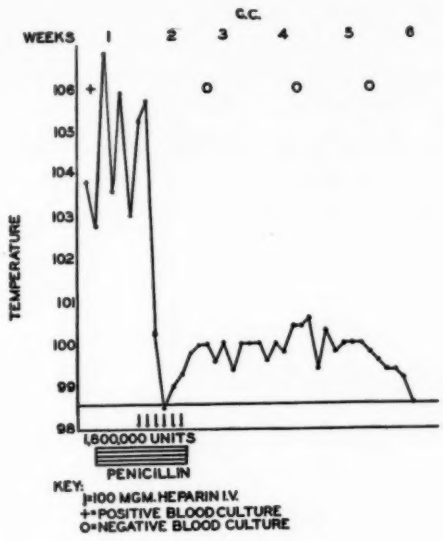
GRAPH XIV



GRAPH XV

bacterial activity for over 6 months; renal findings negative; prophylactic oral surgery; weight gain of 28 pounds, present hemoglobin 98 per cent, ESR 6 mm/hr.

Case–H.C. (Graph XV), age 52, female: (case # 6 of original series[10]); Subacute bacterial endocarditis, Streptococcus hemolyticus; 3 weeks; chronic rheumatic cardiovalvular disease; aortic; widespread, almost lethal embolizations; prompt, dramatic response to penicillin-heparin therapy; progressive clinical improvement and negative blood



GRAPH XVI

cultures, 14 months; present weight 163 pounds, hemoglobin 94 per cent, ESR 7 mm/hr. Has resumed work as a private secretary for past six months.

Case–G.C. (Graph XVI), age 10½, male: Patient with Pneumococcus-type 33 endocarditis referred by Robert E. Gross of Boston and B. S. Denzer for sterilization of the blood stream prior to operation on a patent ductus arteriosus; ill with chills and fever for 3 weeks prior to admission; no response to sulfonamides; progressed favorably following a short course of therapy and was sent home clinically well; temperature chart shows graphically the spectacular response; hyperpyrexia attributed to overwhelming destruction of organisms and consequent liberation of bacterial proteins; when last seen over nine months post-therapy gained 23 pounds, hemoglobin 104 per cent and ESR 3 mm/hr.

CONCLUSIONS

A review of these illustrative cases permits of the following conclusions:

1. Age and sex have no bearing on the outcome of therapy.

2. The type of organism (apart from the so-called Streptococcus sp., Table VI) is immaterial to the outcome of therapy, provided it is inhibitable by penicillin within practical limits (0.007 to 0.25 Oxford units).

3. If the patient is in good physical condition, the duration of the disease less than three months, and the causative organism sensitive to penicillin, a satisfactory result may be anticipated, barring accidents, in virtually every case.*

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* The invitation to address The New York Academy of Medicine during this Graduate Fortnight devoted to a study of the infectious diseases has been a source of tremendous personal satisfaction to me. I should be remiss, however, were I to conclude without expressing my thanks to my various colleagues and collaborators, among whom are included P. Rosenblatt, M. Lederer, H. J. Greene, M. D. Levin, M. Grolnick and E. Alture-Werber, Mr. M. Russell and Misses F. Kashdan and M. Koslof. I would like also to express my gratitude to Harold T. Hyman for his invaluable assistance in the correlation of my data for presentation.

PENICILLIN AND SULFONAMIDES IN THE TREATMENT OF OSTEOMYELITIS AND PYOGENIC ARTHRITIS*

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THE introduction and availability, first of the sulfonamides and now of penicillin, justifies a consideration of the treatment of both acute and chronic pyogenic infections of bones and joints in the light of our present knowledge. This is because some of our previous views on this subject have been modified by the favorable results which we have observed in the use of these antibiotic agents. However, it is realized that our knowledge is still incomplete and that future observations or the introduction of new antibiotic agents may modify the methods of treatment which will be described in this paper. It is also to be noted that this discussion is limited to infections in which the pyogenic staphylococci and streptococci are the offending organisms and these comprise the great majority of the cases in both civil and military practice.

Of the various sulfonamides now available, sulfathiazole is the drug of choice in the treatment of osteomyelitis because it is more active against staphylococci than are the others and it is also effective against streptococci. Statistics indicate that in patients with osteomyelitis over two years of age staphylococci are the causative agent in over 90 per cent of the cases and in infants they are the causative agent in about 50 per cent. Almost all of the remainder are due to streptococci. Sulfadiazine and sulfamerazine have certain advantages in that they are better tolerated by some patients, but these drugs are not as effective as sulfathiazole in staphylococcic infections. Consequently, in this paper only sulfathiazole will be mentioned and it will be assumed that if this drug is not tolerated either sulfadiazine or sulfamerazine may be used.

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In comparing sulfathiazole and penicillin we find that the latter is a more potent antibacterial agent against staphylococci and streptococci, it is effective against a wider variety of organisms, and its toxicity is so low that during its administration the possibility of toxic effects need not be considered. It has the disadvantage that it is not always available, it is expensive and it is not effective when taken by mouth, but must be administered intravenously or intramuscularly or applied locally. It is excreted rapidly and if effective concentration is to be maintained in the blood it should be given by continuous intravenous drip or by intravenous injections at two-hour intervals or by intramuscular injections at three-hour intervals.

Sulfathiazole has the disadvantage that it is not as powerful an antibacterial agent as penicillin and that toxic reactions are frequent and must be watched for while the drug is being taken. These can be minimized by maintaining a large fluid intake and administering thiamine chloride. It has the advantage that it is available, is relatively cheap and is effective when taken by mouth. It can also be used locally and as the sodium salt it can be used intravenously.

Both penicillin and sulfathiazole act directly on the bacteria and the drug must come in direct contact with the bacteria in order to exert its therapeutic effect. For this reason these drugs are most effective against organisms in the blood stream or in areas of cellulitis where there is an abundant circulation in close proximity to the bacteria. In such areas the drug can diffuse into the infected tissues and reach the bacteria in sufficient concentration to exert its effect. The drugs are relatively impotent against localized infections which are surrounded by avascular scar tissue or bone or by a zone of ischemia. In lesions of this type the maintenance of an adequate concentration of the drug in the blood stream will not sterilize the focus because the drug does not enter the focus in sufficient concentration to destroy the bacteria.

It is thus evident that they are especially useful in septicemia and in spreading infections in the soft tissues and bone, but frequently fail to cure or even to favorably affect the course of chronic infections which are well walled off and isolated from the blood stream. However, when the bacteria in chronic foci become active and break through the zone which walls them off and begin to invade the surrounding tissues these drugs may stop the spread of the infection and reduce the focus to its former chronic state. Both drugs are strongly bacterio-

static and even bactericidal when applied locally and for this reason local and systemic treatment should be combined when possible. Fortunately, penicillin and the sulfonamides are not antagonistic and may be used locally or systemically in combination or one drug may supplement or supercede the other without decreasing the effectiveness of either. Finally, occasional staphylococci are resistant to either or both sulfathiazole and penicillin.

Treatment of Acute Hematogenous Osteomyelitis

This is an acute infectious disease which is characterized by a pyogenic focus in a bone and usually this is the most important lesion. There is a variable amount of involvement of the adjacent soft tissues and the bacteria may be present in the blood and metastatic foci may develop. Until it is proved otherwise, it may be assumed that the etiological agent in every case is a staphylococcus or a streptococcus and treatment should be instituted as early as possible on this basis without waiting until the etiology is proved by culture. Fortunately, with the exception of a specific antitoxin for staphylococcic toxemia, the measures at our disposal are effective against both organisms.

The disease varies greatly in severity. It may pursue a relatively mild course and even heal spontaneously without treatment or it may be fulminating in character and the patient may even die of the generalized infection before the local lesion in the bone can be diagnosed clinically. Fortunately, these cases of fulminating septicemia from an obscure focus in a bone are very rare. In the average case the patient is quite sick with high fever, mild septicemia and a definite and recognizable lesion in the involved bone. In the past the mortality was about 25 per cent and a large percentage of the survivors were afflicted with chronic osteomyelitis and the crippling which may result from this disease. By physiological treatment combined with local rest and carefully applied surgery we were able not only to reduce the mortality to about 10 per cent, but to lessen the incidence and severity of the sequelae of the acute disease.

With the advent of the sulfonamides we had, for the first time, an agent which, when administered systemically, was effective against the causative organisms. The more recent discovery and availability of penicillin places in our hands a safer and more powerful antibacterial agent. It is thus evident that our treatment must be revised. Even

before the discovery of the sulfonamides there was a definite trend towards less precipitate and radical surgery and more physiological care of the patient.

Some observers considered acute osteomyelitis a systemic infection of which the local lesion in the bone was only an unimportant part and advised against surgery. I considered the focus in the bone the cause of the toxemia and septicemia and thought that this focus should be drained as early in the disease as the operation could be performed with safety; that is, as soon as the condition could be diagnosed and the patient could be gotten in suitable condition for the operation (Key[1, 2, 3, 4]). It is not surprising that some observers now advocate chemotherapy alone and not only think that surgery is harmful (Baker, Schaubel and Kuhn[5]), but have also discontinued immobilization of the extremity (Hoyt, Davis and Van Buren[6]).

The objectives of treatment are to save the life of the patient, prevent spread of the local disease, clear the blood stream of bacteria, sterilize the focus in the bone, promote healing of the infected and damaged tissues and maintain or restore the health of the patient.

Since the effectiveness of penicillin and the sulfonamides varies directly with the ability of the blood stream to carry the drug to the bacteria, it is important that the treatment with these drugs be instituted as early in the disease as possible, even before the diagnosis can be made if the patient is seen that early. This is in order that the drug may reach the bacteria before extensive necrosis of bone and soft tissue occurs and they become separated from the blood stream by a wide and relatively impermeable zone of necrotic and inflammatory tissue. In a child with fever, localized tenderness, pain and loss of function in one extremity, acute hematogenous osteomyelitis or pyogenic arthritis should be suspected and the patient should be given a full dose of sulfathiaozle immediately and hospitalized as soon as possible. The sulfathiazole should be continued until the symptoms subside or treatment with penicillin can be instituted or a diagnosis of some condition which is not amenable to this treatment is made. Localized joint or bone tenderness, muscle spasm, swelling, heat, redness and fluctuation confirm the diagnosis, but treatment should be instituted before these signs appear. This is not scientific medicine and will cause the drug to be administered to a few patients in whom it is not indicated. but I believe that it will do little harm and may abort many

cases of osteomyelitis.

Unfortunately, in the great majority of instances the nature of the disease is not suspected until the lesion in the bone is well advanced. When the patient is first seen by the surgeon or enters the hospital he has a high fever, is toxic and dehydrated and exhausted by pain and lack of sleep.

When this patient enters the hospital he should be given a sedative if necessary and subjected to a careful, but gentle physical examination in order to determine the nature, location and severity of his disease. Fluids should be given by mouth and physiological salt solution which contains 5 per cent glucose should be administered intravenously until the dehydration has been corrected. Blood should be taken for culture and for matching for transfusion. A white blood cell count, differential count, red blood cell count and estimation of the hemoglobin should be done and the urine examined.

If penicillin is immediately available a full dose (5,000 to 20,000 units) should be given intravenously or intramuscularly as soon after admission as possible and the intramuscular administration of from 2,000 to 15,000 units should be repeated every three hours until improvement is noted. Then the dose may be decreased. In some clinics the penicillin in amounts of from 60,000 to 100,000 units in 24 hours is given by continuous intravenous drip to very sick patients.

If penicillin is not immediately available, a full dose of sodium sulfathiazole should be given intravenously if the patient is very ill (5 to 30 grains) or sulfathiazole by mouth and its administration by mouth or intravenously if necessary in full doses every three hours should be continued until improvement or toxic manifestations justify a reduction in the dosage or until penicillin is substituted. While the patient is taking sulfonamides the urine should be examined daily and the urinary output maintained.

If facilities are available for determination of the level of the drug in the blood, this should be done and the dosage of sulfathiazole and fluid intake so balanced that a level of from 4 to 6 mgm. per cent is maintained. But the fluid intake should not be restricted in order to raise the level of the drug in the blood. This may lead to increased toxicity from the infection and from the drug. Robertson[7] gave from 4 to 9 grams of sulfathiazole daily to children and it is to be noted that children are more tolerant of the drug than are adults.

The affected limb should be immobilized in a large hot wet dressing with a splint or traction if necessary. This dressing should not be changed, except for examination of the part. Its principal functions are to relieve pain and immobilize the extremity. Frequent change of the hot wet dressing defeats both of these objectives. If it is covered with waterproof material the body heat of the patient will keep the dressing warm or hot water bags may be applied around it.

If the patient is anemic a small transfusion of from 100 to 250 cc. of blood should be given and this should be repeated daily until the anemia is corrected. He should be given large amounts of vitamin B and C as long as the disease is active.

In some clinics (Baker[5]) staphylococcus antitoxin is given to combat the toxemia when this is indicated by a marked shift to the left in the differential count of the white blood cells. I have had little experience with this antitoxin, but believe that if properly used it is a valuable agent in the treatment of very ill patients who are toxic from staphylococcic infection. It must not be relied upon to cure the disease because it has no effect upon the bacteria, but merely tends to neutralize the toxins which they produce.

Of the above therapeutic measures, sedation, sulfathiazole or penicillin, immobilization of the part, intravenous fluids and transfusion, if necessary, should be instituted as soon as possible after admission to the hospital and the patient should then be left alone and permitted to rest.

It is noted that the x-ray is not mentioned. This is of no value in the early diagnosis of the disease and the patient should not be subjected to an x-ray examination until a week or more after the onset when sufficient time has elapsed for changes to occur in the bone which will be visible in the roentgenogram.

The question now arises as to whether or not surgery is indicated. In the past I have maintained that the focus in the bone should be drained as soon as the patient is ready for the operation; that is, after the above measures have been instituted and the dehydration has been corrected and he has rested and his general condition has improved to a point where the operation can be performed with relatively little risk. I now think that it is time to reconsider that opinion, because the principal reason for the operation was to relieve the tension in the bone and prevent or lessen the spread of the infection. We now have

sulfathiazole and penicillin which tend to limit the spread of the infection and gradually to lessen the tension in the bone. If treatment is started early it seems probable that these agents can sterilize the focus in the bone and so limit the necrosis of bone that gross sequestra will not form.

On the other hand, if the specific treatment is started relatively late in the disease (4 to 7 days after the onset) it is probable that the focus in the bone is so well established and so extensive that the drug cannot enter the abscess in sufficient concentration to kill the bacteria. Under these conditions it is still my opinion that the focus in the bone should be drained as soon as the patient is ready for the operation and the focus can be identified and approached surgically. In infants (under two years of age) the bones are so porous that operation on the bone is not necessary and the abscess in the soft tissue may be aspirated or drained by a small incision and usually the dead bone will be absorbed and replaced without sequestration. But in older children it is probable that intense chemotherapy or penicillin may cause the acute disease to subside and leave a chronic infected focus in the bone which may flare up when activity is resumed or at some later date. I have seen both of the above sequences of events occur in patients who had been treated elsewhere.

The operation may be done under general or local anesthesia and is a relatively simple and non-shocking procedure. The bone is exposed through the shortest and safest route and the periosteum split and two or more small drill holes are made through the cortex. A small window may then be removed from the cortex but no attempt is made to remove the infected cancellous bone or marrow. Hemostasis is effected, the wound is sprinkled with sulfathiazole powder and packed loosely with vaseline gauze and the extremity is immobilized in a well-padded plaster-of-Paris cast. If penicillin is available the vaseline gauze is put only around the margins and walls of the wound and a small catheter is placed in the depth of the wound and led out through the dressing and the cast and a small amount of penicillin (5 to 10 cc. of a solution containing 250 units per cc.) is instilled into the wound once or twice daily.

Immobilization is a very important part of the treatment and should be continued until the wound is almost healed or until chronic osteomyelitis is present and there is sufficient involucrum to prevent a patho-

logical fracture. The general supportive treatment should be continued as indicated until the improvement in the patient's general condition warrants a return to a normal regime.

It is to be emphasized that the operation is for drainage only and is a relatively mild procedure. When properly performed and rightly timed and followed by effective immobilization of the part, I do not believe that the drainage operation does any harm. I have seen patients in whom the disease appeared to spread widely through the bone and cause extreme destruction and involvement of the adjacent joints and even develop secondary foci while being treated with sulfathiazole. It is reasonable to think that early drainage of the focus in the bone would have lessened the spread of the disease in these patients.

When should the operation be performed? I see no reason for waiting until the temperature is normal and the acute infection has subsided. If the patient's general condition warrants the administration of a local or short general anesthetic (inhalation or pentothal) and the focus can be identified with a fair degree of certainty the focus should be drained. This operation is not performed as an emergency, but is done when the condition of the patient is satisfactory and at the convenience of the surgeon and the staff. In some patients it may be done on the day after admission or even on that day and others may enter the hospital with a severe septicemia and profound toxemia and may die of the infection or recover and the local disease subside without being fit subjects for a drainage operation at any time. If the disease is limited to cancellous bone sequestration may not occur, even in older children with severe infection.

It is possible that further experience with penicillin will cause this opinion to be revised, but I doubt it. When the disease is well advanced dead bone is present and, especially in older children, this will sequestrate and be difficult to sterilize by systemic treatment. The fact that the local and general symptoms have subsided does not mean that the patient is cured of osteomyelitis.

In pyogenic joints the situation is different and a sulfathiazole suspension or, better, penicillin can be injected directly into the joint cavity in sufficient amounts (10,000 to 40,000 units) to kill all susceptible bacteria in the joint and in the synovial tissues. If this is combined with adequate systemic treatment and is done before the cartilage is destroyed, the joint may be saved and a prompt restoration of func-

tion may be expected. The injection is made in sufficient normal salt solution to distend the joint cavity slightly and is repeated daily until the general and local symptoms subside. If the patient is seen late, after the cartilage is destroyed, the joint should be drained and then immobilized in a functional position and local and systemic administration of the drug continued just as was described for the infection in the bone.

Infected compound fractures should be treated roughly as described above, except that adequate drainage followed by reduction and immobilization are important parts of the treatment and the operation should be done as soon as the patient can be gotten in satisfactory condition. If gas bacillus infection is present the appropriate antitoxin may be combined with the penicillin or sulfathiazole and the operation should be performed as soon as possible and the involved muscles excised widely or the extremity amputated if it is devitalized.

The Treatment of Chronic Osteomyelitis

In this condition surgery is usually necessary if the disease is to be cured, but sulfathiazole and penicillin are useful adjuncts to our surgery and are also useful in quieting down acute flare-ups of the chronic infection.

In a chronic osteomyelitis the disease may remain quiescent without drainage or other symptoms over a variable period and the focus may then become painful and acutely inflamed and an abscess may develop and rupture spontaneously unless it is drained. Or a sinus may close spontaneously and then pain, local inflammation and an abscess may develop. As a rule, these acute exacerbations of the disease are not accompanied by much fever, nor is the patient dangerously ill. However, this is not always true and they should not be taken too lightly, because sometimes the disease becomes invasive in character and may cause septicemia and even death.

In the past we have treated these acute exacerbations of the disease by rest in bed, forcing fluids and hot, wet packs and immobilization of the extremity and surgical drainage. Now, with sulfathiazole or penicillin added to the above measures, we frequently see the acute symptoms subside without abscess formation and the patient may again resume work within a relatively short time or he may elect to submit to an attempt to cure the disease by a radical surgical procedure. If abscesses form they should be drained as in the past.

In considering the surgical treatment of chronic osteomyelitis, the operation for cure should be undertaken only while the disease is relatively quiescent; that is, when fever, pain and local signs of acute inflammation are absent. Then, the patient should be hospitalized a day or two before the operation and penicillin or sulfathiazole administered in moderate doses (10,000 units of penicillin intramuscularly every 3 hours or 15 grains of sulfathiazole by mouth every 4 to 6 hours).

The operation should be performed just as carefully and thoroughly as though the drug were not being used and an attempt should be made to remove all sequestra and as much as possible of the dead and infected bone and to saucerize the cavities in the bone and eliminate the dead space. The infected walls of the sinuses are also excised. The wound is then sprinkled with sulfathiazole and sutured and the extremity is immobilized in a plaster-of-Paris cast. Dry penicillin powder may be mixed with the sulfathiazole powder or a small catheter may be placed in the bottom of the wound and the wound sutured around it and penicillin instilled into the wound daily for a week or so after the operation. The systemic administration of the drug is continued for from one to two weeks after the operation, or until the wound is healing. Depending upon the lesion, the cast is removed in from two to four weeks after the operation. Healing and probable cure can be obtained in about 60 per cent of the cases.

In those cases in which the operation fails in that the wound does not heal by primary intention after it is sutured, I have not found that the attempt to close it has precipitated a severe infection, but has resulted in a reduction of the size of the open wound and is followed by one or more sinuses which lead to infected bone. In other instances the wound will be healed when the cast is removed, but it will exhibit signs of infection or sinuses may develop when function is resumed, or at some later date. In these it will be found that the operation has been inadequate. The principal reasons for failure in my hands have been incomplete removal of sequestra, insufficient removal of dead or infected bone, inability to obliterate dead spaces, closure with too much tension and inability to close the wound because of damage to the soft tissues by previous surgery and long continued infection.

The use of adequate surgery within a few months after the subsidence of the acute disease would eliminate a considerable proportion of the severe cases of chronic osteomyelitis with large eburnated bone

containing one or more large cavities and a variable number of small foci of disease. Such cases may be incurable by anything short of amputation and neither sulfathiazole nor penicillin can be expected to solve the problems which they present (Key[8]).

The dead bone should be removed as soon after the subsidence of the acute infection as it can be identified. It is wrong to wait for it to sequestrate or for a massive involucrum to form. The dead bone harbors infection and the massive involucrum becomes chronically infected as it is formed. Even if a pathological fracture is produced or follows the operation, this will do no great harm if the extremity is properly immobilized after the operation. Likewise, even if it is not possible to identify and remove all of the dead bone at the first operation something will be gained and a second or third operation may be performed if necessary. There is no reason why a surgeon should not plan to cure a chronic osteomyelitis by a series of operations, just as a plastic surgeon plans to replace extensive scar tissue by a series of skin grafts. The same is true of infected compound fractures. The surgeon should not wait for many months or years until the infection is almost incurable before attempting to create conditions favorable for elimination of the infection. The re-inforcement of good surgery by sulfathiazole or penicillin justifies a more aggressive attitude on the part of the surgeon in his war on infection in bone. On the other hand, he should do as little harm as possible and avoid the removal of living bone which may aid rather than interfere with healing. It is thus evident that subperiosteal resection is not recommended. Rather, one should perform a meticulous removal of as much dead and infected bone as possible.

From what has been written above it may be inferred that I no longer use or recommend the Orr treatment for chronic osteomyelitis. This is not the case. I both use and recommend it. It is used in wounds which cannot be closed satisfactorily and in wounds in which the infection for some reason seems too virulent to permit primary closure. This is especially true of extensive infections with large sequestra and foul-smelling, brown colored saprophytic pus. These foci are treated as adequately as possible, then sprinkled with sulfathiazole, packed loosely with vaseline gauze and immobilized in a plaster cast, or penicillin may be instilled through a catheter led out through the cast. They usually require one or more operations after the severe infection has subsided and may be closed or not, depending upon the state of

the wound at the end of the operation. The drug is also administered systemically both before and for a week or so after operation.

Conclusion

Acute and chronic osteomyelitis are surgical conditions in which sulfathiazole and penicillin are valuable adjuncts to, but rarely substitutes for sound surgical treatment.

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THE HISTOLOGY OF THE NORMAL AND DISEASED PANCREAS*

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THIS paper does not purport to be a complete review of all existing information on the subject indicated in the title. Since the structure of the pancreatic islets under normal and pathologic conditions is well covered in many textbooks of histology and pathology, in this presentation well known facts will be touched only superficially, and, instead, stress will be laid on some less generally known points, some of which are too recent to be included in textbooks.

The insular system consists of special cells distributed rather irregularly among the pancreatic acini and possessing a characteristic appearance and structure. Their shape is cuboideal, sometimes columnar or wedge-like. With most routine stains their cytoplasm is homogeneous and much lighter than that of the acinus cells because of the absence of both zymogen granules and chromidial substance. That is why larger accumulations of them can be recognized even under low power and with almost any staining technique. Although they can be distinguished from acinus cells by several cytological differences, their most distinctive feature is their specific granulation, demonstrable only with suitable differential stains. These granules set them off sharply from both the acinus and duct cells which are devoid of such granules.

Islet cells form well circumscribed, more or less bulky solid groups of a rather typical structure (islets) but are also found scattered singly or in poorly delimited small groups among the acini and in the lining of small ducts.

The islets can be studied as to number and size by various techniques such as supravital perfusion with neutral red or by planimetric measurement. This latter technique consists in projecting stained micro-

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scopic slides on a paper screen, outlining the islets, cutting them out with scissors, counting and weighing the pieces. In this way the number of the islets and their surface area in terms of percentage of the total surface can be calculated with ease. The important point is to take sections from many different parts of the gland since the distribution of the islets may vary considerably in different portions, although the notion that they are especially plentiful in the tail cannot be substantiated. There are data available concerning the number of islets in the normal human pancreas, and it seems that the range of variation is extremely wide. The total number of the islets in the human pancreas lies between 250,000 and 2,500,000, the majority of the cases being around 500,000. More meaningful is the total area of the islets, expressed in percentages of the total, since this figure includes both size and number of the islets and is actually proportional to the amount of islet tissue. The average normal value for man is 1 to 3.5 per cent. In certain animal species such as the dog and the cat the individual variation is so tremendous and the distribution of the islets in various parts of the gland so freakish that it is practically impossible to give normal values. Especially among dogs extremely low insular counts with almost complete absence of islets in some parts of the pancreas are quite common even under apparently normal conditions. Extreme caution is warranted before statements on changes in the amount of insular tissue, produced by experimental procedures, are made.

In size the individual human islets may range from a single cell to a group of over 300 micra in diameter, although the average islet will have a diameter of 70 to 150 micra.

The islets are composed of anastomosing short cords, usually only one or two cells thick. They are delimited more or less completely against the acinar parenchyma by the basement membranes of the acini and ducts or by the interacinar connective tissue. They do not have a capsule in the strict sense of the word and may be in direct contact with acini. Some islets are in direct continuity with ducts. A special kind of islets are the neuroinsular complexes which are composed of islets in intimate contact with sympathetic ganglion cells. They seem to be constant organites in the pancreases of all species. Nothing is known about their functional significance but the belief has been expressed that they may be chemoreceptors concerned with regulation of the secretion of insulin.

Extrainsular islet cells may be found scattered among the acini. Some of these tiny cell groups may be interpreted as slender peripheral processes of larger islets but individual islet cells, obviously outside of all insular relationship, are often seen wedged in between acinus cells. Other islet cells are embedded in the lining of ducts. These cells are likely to be completely overlooked if only routine stains are used but can be discovered easily in thin sections stained for specific granules. In certain animal species such as the white whale, extrainsular islet cells are very numerous, but they can be found in varying numbers in almost all species. In some human cases large numbers of them can be found both among the acini and in the lining of ducts; in other cases they seem to be completely absent. Unfortunately, quantitative data as to their occurrence under normal and under pathologic conditions are not available, although such data would be of great interest. A high count of extrainsular islet cells could explain such puzzling cases as that of Binger and Keith[1] in which no islets could be found in the pancreas at autopsy although there was no evidence of diabetes in vivo.

Acinus-islet Relationship

The relation between the islets and the acini has been a moot point ever since the discovery of the islets. All histologists agree that both acini and islets are formed from ducts. Also, there can be no doubt that islets are formed in embryonic life by the budding of acini. However, opinions are divided concerning the fixity of the two tissue types once fully developed. One group of workers finds no evidence for acinoinsular transformation and asserts that both acini and islets are specific, noninterchangeable tissues which are capable of further growth or regeneration only by the division of their own cells, besides, of course, by new formation from ducts. Another, equally numerous group has maintained that the relation between islets and acini is dynamic rather than static and that conversion of acini into islets and vice versa does occur under functional stimuli even in the adult organism.

This divergence of opinions is due mainly to the application of too lax criteria to the diagnosis of acinoinsular transformation. Since at times it may be quite difficult to decide on the basis of routinely stained slides whether a particular cell is an acinus or an islet cell, the subjective factor will become of decisive importance in settling the question. This is especially true in cases of regeneration and hypertrophy of the islets

when the acinoinsular boundary may become more or less jumbled. Since the one positive means of identification of both acinus and islet cells is the demonstration of their specific granules, the only cogent evidence for acinoinsular transformation would be the finding, with specific stains, of cells containing both types of granules. If this criterion is accepted, the overwhelming majority of papers championing acinoinsular transformation must be dismissed because their authors failed to demonstrate such cells. The often observed apparent continuity between islets and acini, the lack of delimitation between the two tissues, are mere survivals of embryonic conditions and by no means an evidence for transformation. Being very much interested in the problem I have studied many hundreds of slides of both human and animal pancreases but have never seen a cell intermediate between an acinus and an islet cell either under normal or under pathologic conditions. I also paid attention to the often mentioned transitional forms between centroacinar and islet cells, but the results were negative.

On the other hand, there can be no doubt that islets can be formed from ducts even during adult life. Although in the majority of human pancreases there is very little new formation of islets, in a number of cases all steps of such new formation can be traced. The epithelium of small ducts becomes multilayered, buds form which enlarge and finally become detached from the duct. In my collection I have several cases in which new formation of islets is quite conspicuous. Two of these cases show rather extensive arteriosclerotic changes with hyalinosis of the islets but both without any clinical signs of diabetes. Otherwise no correlation whatsoever could be found between the clinical pictures and the extent of regenerative changes as found at autopsy.

Cell Types

The first observations on the presence of more than one type of cell in the pancreatic islets date back almost fifty years.[2, 3] The foundations of the morphology and of the staining properties of the islet cells were laid down by Lane[4] and Bensley[5] about 35 years ago. They distinguished two cell types in the islet of the guinea pig: the alpha cells whose granules are alcohol insoluble but water soluble and the beta cells whose granules are alcohol soluble but insoluble in most aqueous fixatives. The staining technique used by Lane and Bensley was a rather complicated and capricious one which yielded good results only in the

guinea pig and was practically unusable in other species. A minimal change in the composition of the fixative produced color effects very different from those described by the authors, in fact, quite often a complete reversal of the staining reaction so that now the alpha cells stained as the betas should and vice versa. The same applies to a number of similar stains developed on the analogy of Lane's so-called neutral gentian. This inconsistency of results led to a considerable confusion, and it may be said that all papers based on the results of the Lane-Bensley staining technique are of somewhat doubtful value unless they come from the authors themselves or from their pupils who are thoroughly familiar with the knacks and pitfalls of the technique. The Mallory-Heidenhain stain if used on very fresh and properly fixed tissue gives a brilliant picture of the islets in practically all species. The alpha cells show ruby-red granules, the beta cells indistinct orange-grayish ones, and a third type of cells, Bloom's D cells,[6] sky blue ones. Curiously, in the guinea pig the color effect of the alpha and beta cells is reversed in that the alpha cells are orange and the beta cells red.

The chromium hematoxylin-phloxin stain I described several years ago[7] seems to be, on the basis of my own experience and of that of many other pathologists, a very reliable and easy stain that will differentiate with great clarity the dark blue staining beta cells from the red staining alpha cells. The D cells cannot be recognized as such with this stain because they stain very much like the alpha cells. The chromium hematoxylin-phloxin stain works equally well in all of the 20-odd species I examined, ranging from man to the pigeon and the frog. Almost any fixative will do, with the exception of alcohol, although with fixatives containing mercury salts certain corrective measures have to be taken before the staining technique can be applied with good success. The material need not be very fresh if one is not interested in fine cytologic details; very satisfactory counts can be done on tissues fixed as late as 6 to 8 hours, sometimes even 12 to 16 hours after death.

When these two stains, the Mallory azan and the chrome hematoxylin-phloxin stain, are applied to pancreases of the most varied species it is found that alpha and beta cells are invariably present in the islets of all of them. Although there are reports that the D cells are also a universal constituent of the islets of most species, I found easily stained, clearcut specimens only in the pancreas of man and the guinea pig. Occasional bluish staining cells are seen in the islets of many

species but I am not quite sure whether they are actually analogous to the D cells of man and the guinea pig. There are absolutely no transitions between alpha and beta cells. On the other hand, the alpha and D cells do not seem to be two strictly different types since transitional forms are often seen. It is my impression that the D cells develop from the alpha cells through the aging of the latter. Besides these granular cells a number of agranular ones can be found in the pancreases of most species. The majority of these agranular cells are, no doubt, degranulated specimens of the three granular types.

In the islets of some species (guinea pig, dog) the different cell types are intermingled without any recognizable pattern; in others they tend to cluster together in a characteristic way. For instance, in the rat and the mouse the alpha cells occupy the periphery of the islets, while in the horse and in the cat, the center. In human islets the alpha cells often have a tendency to nestle against capillaries while the beta cells occupy the most avascular areas.

In most species the B cells greatly outnumber the alpha cells. Actual counts are available only on human and canine material. In normal human islets around 60 to 90 per cent of all cells are betas, 2 to 8 per cent are D-s, and the remainder alphas. Considerable individual variation in the differential count even between islets within the same slide is quite common. The extrainsular islet cells are mostly alphas.

Both in the human and in animal islets there is a considerable variability in regard to the extent and the degree to which the cells are granulated. However, islets of the same individual usually show the same degree of granulation or degranulation. Considerable degranulation, especially of the beta cells, is a common finding even under apparently normal conditions. Three types of degranulation are encountered in human material: (1) the diffuse, (2) the discontinuous degranulation, and (3) margination. Nothing is known about the importance and meaning of these various states of degranulation, although it is known that acutely high blood sugar levels tend to produce degranulation.

There is a large number of observations available on the effects of various acute and chronic stimuli on the islets. Most of these changes were studied with routine stains only or with the aid of the Lane-Bensley stains, and in many cases it is admitted that the results were very hard to interpret. The overwhelming majority of these observa-

tions are of doubtful scientific value owing either to lack of adequate controls or because the conclusions were based on impressions rather than on sound statistical evaluation of the data. I do not want to go into details of these reports but shall limit myself to the mentioning of a few well established facts. First, the administration of glucose causes an acute degranulation of the beta cells in the guinea pig.[8] In the dog no such changes could be produced even with excessive doses of glucose. Partial ablation of the pancreas invariably, and ligation of the main duct often, cause hypertrophy of the islets. Starvation and pregnancy may also lead to considerable hypertrophy.

Diabetes

The literature on the changes of the islets in human diabetes was so thoroughly covered in Shields Warren's book[9] and so well known to pathologists that I shall not go into details but shall bring out only some important points.

Although certain degenerative changes such as profound reduction in the amount of islet tissue, fibrosis, hyalinosis, lymphatic and hemorrhagic infiltration of the islets, along with certain cytologic alterations such as nuclear pyknosis and hydropic vacuolation can be considered rather typical of diabetes, there are a great many cases on record in which severe diabetes had been present in life, yet at autopsy the islets looked perfectly normal; in fact in some cases there were distinct signs of hyperplasia of the insular system. On the other hand, the pancreas may exhibit extensive degenerative changes quite typical of diabetes, without any in vivo disturbance of carbohydrate metabolism. The reasons of this puzzling inconsistency between the clinical and pathologic findings are so well given by Warren and Root[10] that I shall quote from their paper verbatim:

"Whatever the cause may be, it seemingly acts over a long period of time, perhaps throughout the duration of the disease. The pathology which we find in the pancreas at autopsy rarely represents the initial damage to the organ, but rather the result of a long struggle between the regenerative activity of the pancreas and the degenerative changes caused by the diabetogenic factor. The pancreas is not a static organ like the brain or myocardium, unable to repair itself after injury.

"For some reason this static conception of the pancreas has become firmly established in spite of clinical and anatomical evidence to the

contrary, probably because the diabetic patient cannot be cured and frequently goes steadily downhill in spite of treatment. We believe that this unfavorable course of the disease is not due to failure of the pancreas to regenerate but to continued injurious action on the organ by the causal agent, eventually overcoming the regenerative efforts.

"A transient injury to the islands may explain the severe drop in sugar tolerance noted in diabetic patients during acute infections. The rapid reestablishment of the former level of sugar tolerance following recovery from the acute process may well represent the result of the rapid regeneration of the island cells."

To this I wish to add the following remark: the appearance of the clinical symptoms of diabetes depends only on the inability of the pancreas to supply a sufficient amount of insulin. We know from both experimental and clinical observations that the demand for insulin may vary tremendously under abnormal conditions. It seems that in experimental pituitary diabetes the pituitary extract acts mainly by reducing the efficiency of insulin in some unknown way, thereby increasing the demand. Clinically we have the so-called insulin-resistant cases of diabetes whose insulin requirement may be many times the amount calculated as normal for an adult individual. Even a perfectly normal pancreas may be unable to satisfy such demands. Therefore, all gradations between an absolutely incompetent insular system and a normal one that is relatively insufficient only in the face of excessive demand, are possible.

I hoped that the application of specific stains to diabetic pancreases may shed some additional light on the pathology of this disease. However, the results were disappointing. True, in some cases where the islets looked normal with routine stains, they proved to be very abnormal when stained for cell types in that the beta/alpha ratio was very low or beta cells were absent altogether. On the other hand, a great many cases gave a perfectly normal differential count. It is interesting to note that the beta cells may be well preserved even in greatly shrunken, hyaline islets. Summarizing the present status of the problem of the pancreatic pathology of diabetes, it may be said that although certain changes are highly suggestive of diabetes, it is impossible either to rule out or to confirm the diagnosis of diabetes with certainty on the basis of histologic findings.

The most important contribution to the pathology of diabetes has

been obtained from studies on various types of artificial diabetes. There are three types of induced diabetes known: the surgical, the pituitary and the chemical (alloxan) diabetes. The changes in surgical and pituitary diabetes consist of initial hyperplasia of the islets, followed by degranulation, vacuolation and ultimate disappearance of the beta cells, with fibrosis of the islets as the end stage. As to one of these changes, vacuolation, it should be remarked that it seems to be the expression of acute strain on carbohydrate metabolism. Conspicuous vacuolation may be seen in the pancreases of individuals who died with very high blood sugar levels. Within the last two years I had the opportunity to examine a fair number of biopsy specimens of pancreases. In three pancreases coming from individuals who had received very large amounts of glucose preoperatively vacuolation of the beta cells was a prominent feature. In both surgical and pituitary diabetes the alpha cells escape injury. The changes mentioned seem to be brought about by exhaustion of the insular tissue due to overwork. The proof for this theory is that both surgical and pituitary diabetes can be prevented if the islets are protected in the early stages of the disease by a low carbohydrate diet or by the administration of insulin. On the other hand, alloxan seems to kill the beta cells promptly, without any initial stimulation. Alloxan diabetes cannot be prevented either with a diet low in carbohydrate or by the administration of insulin. The pathologic changes are practically identical in all species.[11] Within a few hours after the injection of alloxan the beta cells become pyknotic. Later the cell cords become fragmented or coalesce into a homogenous debris in which individual cells cannot be recognized. In the course of the next two or three days the necrotic cells disappear without the slightest inflammatory reaction. They become replaced by proliferating alpha cells and by agranular cells only, the beta cells being completely gone. In the dog, the insular changes are accompanied by an extensive vacuolation of the epithelial lining of the small ducts, a change observed also in surgical and pituitary diabetes. This change may indicate that in the dog the duct cells are functionally related to the islets. There is no tendency to recovery from alloxan diabetes, except in rabbits. Rabbits whose diabetes shows improvement usually have a number of more or less normal beta cells preserved in their islets. These cells often show profound vacuolation, a picture similar to that seen in pituitary diabetes.

Finally, I wish to say a few words about islet cell tumors. Their

pathology was thoroughly covered by the excellent review of Duff and Murray;[12] here I want to call your attention to a few important points only. Not all islet cell tumors are functionally active; in fact only about 20 per cent of them are associated with attacks of hypoglycemia. There are over a hundred cases of functional islet cell tumors on record of which only 30 were studied by specific stains and out of this number adequately only 5 or 6. Owing to this small number of well studied cases it is impossible to tell whether functional tumors have a cellular composition different from that of nonfunctional ones. It would be very useful to establish a registry of islet tumors on the example of the Bone Tumor Registry for the purpose of making the comparative study of large numbers of islet tumors possible. On the basis of the few cases I had the opportunity to study, it would seem that although some of the functional tumors do contain cells more or less similar to the normal types, others consist only of cells that contain no identifiable granules.

Comment

According to all experimental and pathologic evidence, the beta cells are concerned in some important way with the regulation of carbohydrate metabolism. However, it is by no means proven, although probable, that they actually secrete insulin and that the beta granules are the morphologic expression of insulin content. In fact, insulin precipitated from commercial solutions by histologic fixatives does not show the staining properties of beta granules; furthermore, tumors with no demonstrable beta cells were found to have a high insulin activity. Therefore, the part played by the beta cells in carbohydrate metabolism is poorly understood. The function of the alpha cells is entirely in the dark.

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Discussion by DR. PAUL KLEMPERER, Pathologist, Mt. Sinai Hospital of papers presented by Dr. Martin G. Goldner and Dr. George Gomori.

I am sure I voice the sentiment of the audience if I express our gratitude for tonight's splendid presentations. The research on alloxan diabetes, stimulated by the original observations of the British authors, has been greatly advanced by the remarkable contributions of Drs. Goldner and Gomori. Their painstaking cytologic studies have clarified the site of the cellular damage in the Islands of Langerhans the complete necrosis of which had originally been reported by Dunn and his coworkers. With the discovery of the selective damage of the B cells by alloxan their significance in the formation of insulin is now more firmly established than before. Beyond that, their investigations have demonstrated that the alteration of the B cells is not the result of overstimulation, as in the other forms of experimental diabetes, but the effect of direct injury by alloxan. This evidence, of course, must challenge our curiosity as to the possible mode of action of alloxan upon the B cells. Is there any answer or any suggestion to account for the destruction of these cells? I wonder if and how the action of alloxan can be inhibited. Is there any interference with enzymatic activity of these cells which could be demonstrated histologically? What is the effect of subtoxic doses of alloxan over a long period? The evidently constant absence of an inflammatory reaction in the vicinity of the damaged Islands of Langerhans seems to me a worthwhile problem although it might not be of particular significance to those primarily interested in

the diabetogenic action of alloxan. But from a general pathologic point of view, it is a provocative observation and I wonder whether our speakers could give us some of their ideas on this puzzling phenomenon. In line with this evidently well established feature of the alloxan pancreas, I should like to refer to the reports of Dunn and his co-workers who found a striking diminution and even absence of Islands in the late phases of alloxan administration. In some preparations which were shown to me by Dr. Wachstein, I had the same impression. Dr. Gomori did not mention such a disappearance of the Islands, and I wonder whether we were mistaken. Of course, the fact that the A cells are not affected by alloxan certainly makes it difficult to understand that the entire Island should disappear and it might well be possible that the small group of surviving A cells can be overlooked.

There seems to be a fundamental difference to the liver picture in A. P. E. diabetes where the liver is devoid of fat except in those cases in which the A cells are also affected, as reported by Ham and Heist. I wonder if the speakers could enlighten us on this feature of A. P. E. diabetes and, in particular, if they also found occasional A cell degranulation in A. P. E. diabetes as seen by Ham and Heist. The absence of A cell damage in alloxan poisoning has been stressed by the speakers. It is, therefore, interesting to note that the liver of the experimental animals showed extensive fatty changes.

The constant sequence of hyperglycemia, hypoglycemia and permanent diabetes following alloxan administration has been one of the most puzzling phenomena. The conclusion arrived at by Drs. Goldner and Gomori as being the result of an action of alloxan upon the adrenals seems to me a brilliant explanation of the hitherto confusing issue.

Dr. Gomori has refrained from drawing any conclusion as to human diabetes from the investigations on alloxan diabetes. I understand his reluctance. Histologic examination of the pancreas, especially in reference to cytologic details, is very disappointing due to the interfering post-mortem changes. I believe that the principles which govern experimental diabetes also operate in human diabetes. But the demonstration of the mode of action by a correlation of the disturbed function with structural alteration which has given us so much insight in experimental diabetes, is unfortunately not so successful in human pathology. It is for this reason that we are usually frustrated if we are asked to explain diabetes by the demonstration of structural alterations. In

fact, we have no reliable histologic criteria for the pathologic diagnosis of diabetes. The hyalinization of the Islands of Langerhans is not found in the majority of cases and might be present without clinical evidence of diabetes. Parenthetically, I should like to ask Dr. Gomori whether he is in agreement with a recent paper by Aronheim who claims that the hyaline material is amyloid. As to extrapancreatic lesions in diabetes, I should like to remind you of the reports by Kimmelstiel and by Allen and Siegel from the laboratories of Mt. Sinai Hospital who found the characteristic intercapillary glomerulosclerosis in about 30 per cent of cases of diabetes. These findings are in my opinion valuable histologic criteria for the diagnosis of human diabetes. It might be worth while to study the kidneys in prolonged experimental diabetes of all types for similar findings.

In conclusion, I should like to say that the correlation of functional aberration with structural alteration has been one of the cornerstones of scientific medicine. If the dramatic discoveries of pure biological sciences have overshadowed the modest contributions of morphology to medicine in recent years, tonight's presentation of Drs. Goldner and Gomori proves that the old method of visualization if properly used is not an antiquated weapon in the arsenal of science.

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